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Published in:
Environment International

DOI:
[10.1016/j.envint.2020.105895](https://doi.org/10.1016/j.envint.2020.105895)

Publication date:
2020

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Han, C., Oh, J., Lim, Y-H., Kim, S., & Hong, Y-C. (2020). Long-term exposure to fine particulate matter and development of chronic obstructive pulmonary disease in the elderly. *Environment International*, 143, [105895]. <https://doi.org/10.1016/j.envint.2020.105895>



Long-term exposure to fine particulate matter and development of chronic obstructive pulmonary disease in the elderly

Changwoo Han^{a,1}, Jongmin Oh^{b,1}, Youn-Hee Lim^c, Soontae Kim^d, Yun-Chul Hong^{e,f,g,*}

^a Department of Preventive Medicine, Chungnam National University College of Medicine, Daejeon, South Korea

^b Department of Occupational and Environmental Medicine, Ewha Womans University of Medicine, Seoul, South Korea

^c Section of Environmental Health, Department of Public Health, University of Copenhagen, Denmark

^d Department of Environmental and Safety Engineering, Ajou University, Suwon, South Korea

^e Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, South Korea

^f Institute of Environmental Medicine, Seoul National University Medical Research Center, Seoul, South Korea

^g Environmental Health Center, Seoul National University College of Medicine, Seoul, South Korea

ARTICLE INFO

Handling editor: Xavier Querol

Keywords:

Cohort studies

Particulate matter

Chronic obstructive pulmonary disease

Age

ABSTRACT

Background: Studies evaluating the role of long-term exposure to fine particulate matter (PM_{2.5}) on chronic obstructive pulmonary disease (COPD) development showed inconsistent results and were limited to Western countries. We aimed to determine the association between long-term exposure to PM_{2.5} and COPD development in metropolitan cities in Korea, which have higher PM_{2.5} levels than those in Western country studies.

Methods: We constructed a retrospective cohort (elderly aged over 65 years who resided in 7 metropolitan cities in 2008) using Korea health insurance data. A total of 687,940 elderly who had not visited hospitals due to COPD for 3 years (from 2008 to 2010) were followed-up from 2011 to 2016. The first hospital visit due to COPD during the follow-up period was regarded as COPD development. Daily district-level PM_{2.5} concentrations were estimated by chemical transport model and 60-month moving average PM_{2.5} were assigned to each subject in time-varying Cox proportional hazard model.

Results: The mean concentration of modelled PM_{2.5} in 7 metropolitan cities during the study period (from 2006 to 2016) was 28.0 µg/m³ and 259,700 subjects newly visited the hospital due to COPD. COPD hospital visit hazard ratio for a 10 µg/m³ increase in 60-month moving average PM_{2.5} concentration was 1.09 (95% confidence interval: 1.07, 1.11). Risks remained unchanged following different PM_{2.5} exposure levels (48-month moving average, and average PM_{2.5} concentrations for 2008 and 2008–2010) and in subgroup analysis by subject characteristics (sex, age, and income groups).

Discussion: By following-up 687,940 elderly subjects who resided in metropolitan cities in Korea for 6 years, long-term PM_{2.5} exposure showed association with COPD development.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by airflow limitation and disruption of lung parenchyma with progressively worsening cough and breathlessness (Pauwels et al. 2001). Although the major risk factor is cigarette smoking, environmental factors such as household and ambient air pollution exposure and occupational dust and chemical exposure are believed to play a considerable role in disease pathogenesis (Pauwels et al. 2001; Salvi and Barnes 2009). For example, household air

pollutants arising from the use of solid fuels may cause inflammation and oxidative stress to the bronchial epithelium and lung parenchyma, which leads to airway obstruction and disruption of the lung parenchyma (Silva et al. 2015). Recent meta-analysis has shown an increased risk of COPD and chronic bronchitis among household solid fuel users (Kurmi et al. 2010). Several intervention studies in developing countries showed improved chronic respiratory symptoms after reducing household air pollution levels, suggesting a close association between household air pollution and COPD development (Gordon et al. 2014).

* Corresponding author at: Department of Preventive Medicine, Seoul National University College of Medicine, 103 Daehangno, Jongno-gu, Seoul 110-799, South Korea.

E-mail address: [ychong1@snu.ac.kr](mailto:yhong1@snu.ac.kr) (Y.-C. Hong).

¹ Changwoo Han and Jongmin Oh contributed equally to this study.

<https://doi.org/10.1016/j.envint.2020.105895>

Received 16 December 2019; Received in revised form 26 April 2020; Accepted 27 April 2020

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Although the overall exposure levels, toxicities, and types of pollutants differ from those of household air pollution, several cohort studies in the U.S. and Canada showed increased COPD and respiratory mortality after long-term exposure to ambient air pollution (Lepeule et al. 2012; Lipsett et al. 2011; Pinault et al. 2017). Based on the study results, the World Health Organization (WHO) estimated that globally over 76,500 COPD deaths were attributable to ambient particulate matter less than 2.5 μm in diameter ($\text{PM}_{2.5}$) exposure, in 2016 (World Health Organization 2018). Based on the Global Burden of Disease estimates, 27.1% of COPD mortality in the world were attributable to ambient $\text{PM}_{2.5}$ exposure in 2015 (Cohen et al. 2017).

However, most of the previous ambient air pollution and COPD studies focused on mortality instead of intermediate health outcomes such as hospital admission or ambulatory care. Although few studies reported the long-term effects of $\text{PM}_{2.5}$ on the initiation of COPD by using hospital admission records, the results were inconsistent (Andersen et al. 2011; Atkinson et al. 2015; Gan et al. 2013; Guo et al. 2018). In addition, most of the previous studies were conducted in the Western countries where annual $\text{PM}_{2.5}$ concentrations are below the WHO guideline value of 10 $\mu\text{g}/\text{m}^3$. Therefore, evidences regarding the effects of long-term exposure to ambient air pollution on COPD development are still limited and inconclusive, especially in high $\text{PM}_{2.5}$ concentration ranges.

Therefore, we evaluated the association between long-term exposure to $\text{PM}_{2.5}$ and COPD development in elderly population in Korea, where $\text{PM}_{2.5}$ levels are higher than those in Western countries. Due to the high incidence rate of COPD among aged population, we focused on the elderly aged over 65 years in our study. By constructing a population cohort based on Korea health insurance data, we were able to secure the largest number of elderly subjects compared to previous studies.

2. Methods

2.1. Study design and population

The present study constructed a retrospective cohort based on the data from the National Health Insurance Database (NHID) in Korea. Due to the single-payer health insurance system, the NHID archives all the hospital service information including the date of hospital use, primary and secondary diagnostic codes (International Classification of Disease, 10th revision code), and procedures and medication use during the hospital service for almost the entire Korean population (over 97%). The database also contains the yearly characteristics of the insurance policy holder or dependents including age, sex, household income, and district-level residential information. A detailed explanation of NHID was published previously (Seong et al. 2016). Based on the researchers' requests, the National Health Insurance Service (NHIS) customizes the NHID (customized dataset) and provides to the researchers.

We designed our dataset focusing on the elderly population residing in 7 metropolitan cities (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) in Korea with 3 years of wash-out period (from 2008 to 2010, to define previous COPD-related hospital use) and 6 years of follow-up period (from 2011 to 2016, to define COPD development) (Fig. 1). Due to the data provision policy of NHIS regarding the size of the customized data, we could only obtain hospital use data for elderly subjects residing in metropolitan cities in Korea for limited disease outcome (COPD) and time period (for the years 2008 to 2016).

Among the entire elderly population who were aged over 65 years in 2008 ($n = 1,720,230$), we restricted our study subjects to those who: 1) maintained the NHIS qualification during the study period; 2) was still alive during the wash-out period; 3) had lived in a metropolitan city in year 2008, and 4) had maintained the same address during the study period 2008–2016. After further excluding subjects who used the hospital due to COPD during the wash-out period ($n = 328,076$), we followed-up 687,940 subjects with no prior history of COPD hospital

visits. Based on the district-level residential data of each subject, we assigned $\text{PM}_{2.5}$ exposure data to each subject. This study was exempted from review by the Institutional Review Board of the Seoul National University Hospital (E-1807-038-956) because we used de-identified data provided by NHIS and had complied with the NHIS personal information protection guideline.

2.2. COPD hospital visits

We used the International Classification of Disease, 10th revision codes to define hospital visits due to COPD (J40–J44). If subject's primary or secondary diagnostic code for hospital visit was coded as COPD, we regarded it as a COPD hospital visit case. We did not separate the mode of visits (emergency or non-emergency), types of hospital (primary or tertiary), and types of medical service (admission or ambulatory care) in the analysis to screen all the COPD related hospital visits.

2.3. $\text{PM}_{2.5}$ exposure data

The study subjects were assigned to district-level $\text{PM}_{2.5}$ concentrations based on their residential information in the NHID. We utilized the Weather Research and Forecast (WRF, version 3.3.1) - Sparse Matrix Operator Kernel Emission (SMOKE, version 3.1) - Community Multiscale Air Quality (CMAQ, version 4.7.1) model to estimate meteorology, chemistry, and emission over Korea. This model enables researchers to estimate short as well as long term $\text{PM}_{2.5}$ trend in a district-level. The details and validity of the $\text{PM}_{2.5}$ modelling data are summarized in previous papers (Kim et al., 2017a, 2017b). In brief, air quality was simulated by CMAQ model (with AERO5 aerosol module) and version 99 Statewide Air Pollution Research Center (Byun and Schere 2006). Meteorology was simulated by using WRF with the National Center for Environmental Protection Final data (Skamarock and Klemp 2008). The meteorology was further processed with the Meteorology-Chemistry Interface Processor (MCIP, version 3.6) for CMAQ modelling (Otte and Pleim 2010). Anthropogenic and biogenic emissions were simulated by using the SMOKE processing Korean National Emissions Inventory data (Clean Air Policy Support System 2010) and by using the Model of Emissions of Gases and Aerosols from Nature (MEGAN), respectively.

Two model domains, sized 27-km (covering northeast Asia) and 9-km, were used in our analysis. The 27-km modelling domain simulation results were used to estimate the boundary condition for the 9-km domain. We first simulated the hourly concentration of $\text{PM}_{2.5}$ at the grid level and resampled the values to the district-level based on the GIS shape file. By comparing modelled data with observation data from the monitoring station (for year 2015 to 2016 when the monitoring data were available), the correlation coefficient was over 0.95. We were unable to use the monitoring data in our study because district-level $\text{PM}_{2.5}$ monitoring in metropolitan cities in Korea began in 2015.

The district level $\text{PM}_{2.5}$ exposure levels were linked to each subject as follows. First, the daily average $\text{PM}_{2.5}$ levels in each district of metropolitan cities were estimated using the chemical transport model. Then, for each month during the follow-up period, the 60-month and 48-month moving average exposures of $\text{PM}_{2.5}$ were calculated and assigned to each subject (Dekker et al. 2008). Although we have 6 years of hospital use data from year 2011 to 2016, $\text{PM}_{2.5}$ modelling data were only available from year 2006. Therefore, the longest time period to address the chronic effect of $\text{PM}_{2.5}$ exposure was 5 years (60 months) and we selected 48 months for the sensitivity analysis. In addition, average exposure values for year 2008 and 2008 to 2009 based on the residential address were calculated and assigned to each subject for the sensitivity analysis using Cox proportional hazard models.

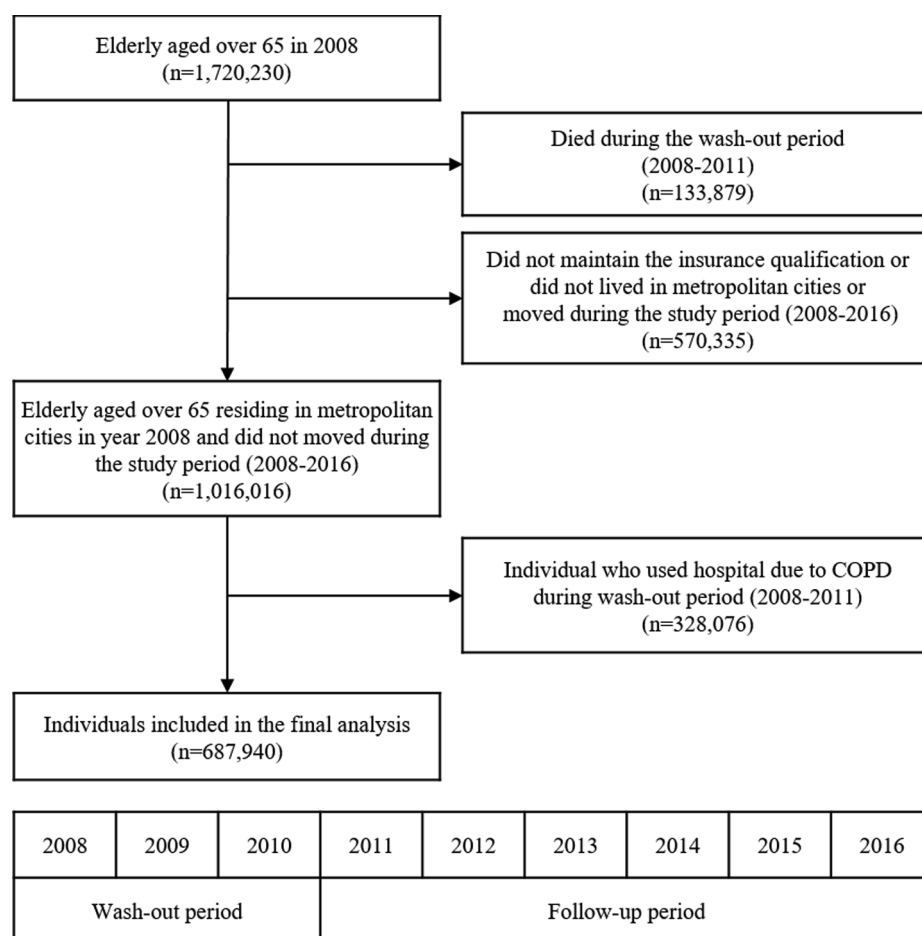


Fig. 1. Flow chart for study population who met inclusion and exclusion criteria.

2.4. Covariates

We extracted the following personal level data for the year 2008 from the customized dataset of NHID: age (years), sex (men or women), and household income. The NHID provides household income on a scale of 1 to 20 (1 being the lowest and 20 the highest). Based on this income scales, we classified the household income into 4 groups (Q1, 1–5; Q2, 6–10; Q3, 11–15; Q4, 16–20). Contextual variables as used in previous studies were selected to adjust for neighborhood and regional effects on subjects' health in our analysis model (Gan et al. 2013; Pinault et al. 2017). We selected data for the district-level proportion of subjects with high school diploma (%), proportion of current smokers (%), monthly average income (1,000 KRW), and standardized mortality rate (per 100,000 person). The data, nearest to 2008, the start year of our study, were acquired from publically accessible database. Proportion of current smokers in each district for year 2010 was acquired from the Community Health Survey results while the proportion of subjects with high school diploma and standardized mortality rate for year 2010 were acquired from Korea Statistical Information Service (Kang et al. 2015; Statistics Korea 2018). The monthly average income data for year 2016, which was the nearest data to that of 2008, were retrieved from the National Pension Service (National Information Society Agency 2018). Descriptive statistics of district-level covariates in 7 metropolitan cities are summarized in Table S1.

2.5. Statistical analysis

We constructed time-varying Cox proportional hazards models to estimate the effects of chronic $PM_{2.5}$ exposure on COPD hospital visits

(Dekker et al. 2008). The time-varying Cox proportional hazard model enables researchers to estimate the effects of time-dependent risk factors (e.g. $PM_{2.5}$) on health outcomes (e.g. COPD-related hospital visit). In conventional survival analysis, we are estimating the chronic effects of certain risk factors evaluated at a certain time point by assuming that the risk factors do not change over time. However, the $PM_{2.5}$ exposure level assigned to each subject may change due to the long-term trends and daily fluctuation of $PM_{2.5}$ levels. To address this issue, the time-varying Cox proportional hazard model used in our study calculates the hazard ratio (HR) for moving average $PM_{2.5}$ concentration in each monthly time intervals and was weighted averaged to generate single HR value.

The follow-up time (in months) was calculated from the start of the follow-up period (January 2011) until the first COPD-related hospital visit or death or the end of the study period (December 2016), whichever came first. The 60- and 48-month moving average $PM_{2.5}$ concentrations were assigned to each study subject in monthly intervals during the follow-up period. The hazard ratios (HR) per $10 \mu g/m^3$ increase in 60- and 48-month moving average $PM_{2.5}$ were calculated. The analysis model was stratified by sex and age (5 yearly intervals, 65–69, 70–74, 75–79, 80–84, and ≥ 85 years), thereby having own baseline hazards and adjusted for personal- and contextual-level variables selected a priori. In model 1, we adjusted for year 2008 household income (4 groups) and residential region (metropolitan city). In model 2, we further adjusted for district-level contextual variables: proportion of subjects with high school diploma, proportion of current smokers, monthly average income, and standardized mortality rate for each district.

We conducted stratified analysis by sex, age group (65–69, 70–74,

75–79, 80–84, and ≥ 85 years), and income groups. The interaction terms between PM_{2.5} concentration and baseline characteristics (sex, age, and income groups) were constructed to evaluate for potential effect modification in both model 1 and model 2. The exposure–response curve between 60-month moving average exposure to PM_{2.5} and COPD hospital visits was plotted using the natural cubic splines (3 knots presented at 0.05, 0.50, 0.95 percentiles of PM_{2.5} concentration). We also constructed Cox proportional hazard models to estimate the effects of baseline PM_{2.5} exposure levels on COPD development, instead of using time-varying moving average PM_{2.5} exposure. The year 2008 to 2010 and year 2008 average PM_{2.5} exposure levels were assigned to each study subject. The stratification and covariates used in the analysis were identical to the time-varying Cox proportional hazards models.

A series of sensitivity analyses were conducted to evaluate the robustness of our study findings. First, we changed the study period by increasing the wash-out period (from 2008 to 2013) and decreased the follow-up period (from 2014 to 2016) to apply more strict criteria (no prior COPD-related hospital visits occurred during the previous 6 years) to define COPD incidence case. Secondly, we applied random effect of metropolitan cities in multilevel time-dependent Cox model to see the potential clustering effect by metropolitan city. Thirdly, we applied different COPD hospital visit definitions by focusing on the primary COPD diagnostic code or by regarding subjects with two or more COPD hospital visits as a COPD development case. Last, we did not restrict the study participants to those who maintained the same address and therefore, included all the subjects who maintain the health insurance qualification during the study period and conducted the analysis. All the analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R statistical software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at a p-value of less than 0.05.

3. Results

The demographic characteristics of the study population are presented in Table 1 and Table S2. Among 687,940 subjects, 58% were women, majority were aged 65–69 years, and belonged to the highest income group. During the 6 years of follow-up, 259,700 subjects (37.8%) were newly diagnosed with COPD and the overall average follow-up time for all subjects was 50.1 months. Overall incidence rate by metropolitan cities were from 34.6 (Daejeon) to 43.4% (Busan) (Table S2).

The spatial and temporal yearly PM_{2.5} concentration trends in the metropolitan cities in Korea are presented in Table 2. The mean concentration of the modelled PM_{2.5} in the 7 metropolitan cities during the year 2006 to 2016 was 29.0 $\mu\text{g}/\text{m}^3$ while the overall PM_{2.5} concentration was decreased in all metropolitan cities in Korea during the period.

Table 3 shows the HR of COPD hospital visits for each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} exposure levels. After stratifying by age and sex; and adjusted for household income groups, metropolitan city, and district-level covariates, a 10 $\mu\text{g}/\text{m}^3$ increase in 60-month moving average PM_{2.5} was associated with an elevated risk of COPD hospital visits of 1.09 [95% confidence interval (CI): 1.07, 1.11]. By using year 2008 to 2010 average PM_{2.5} exposure levels, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with an elevated risk of COPD hospital visits of 1.07 [95% CI: 1.05, 1.10]. The analysis with 48-month moving average and year 2008 baseline PM_{2.5} exposure showed similar results. The exposure–response curve between 60-month moving average PM_{2.5} exposure and risks of COPD hospital visits is presented in Fig. 2. The risk of COPD hospital visits increased as PM_{2.5} exposure increased, showing an increasing linear pattern after 30 $\mu\text{g}/\text{m}^3$ concentration ranges. There was no increase in risks at concentration ranging from 20 to 30 $\mu\text{g}/\text{m}^3$.

In sex- and incomes-stratified group, effect estimates were slightly higher in women (p-value for interaction: 0.16) and in the high income

group (p-value for interaction: 0.25) (Table S3 and S4). In age-stratified group, the effect estimates increased continuously with increasing age, but those aged 85 years or older showed null results (p-value for interaction less than 0.01). In a sensitivity analysis with different wash-out period, the random effect of metropolitan cities, and different COPD definitions showed similar results with our main analysis results (Table S5, S6, and S7). When we did not restrict the study participants to those who maintained the same address, we found similar results to our main analysis (Table S8).

When we changed our definition of COPD development to that of subjects with two or more hospital visits due to COPD during the follow-up period, 171,961 subjects (25.0%) were newly diagnosed with COPD. We found similar results with the main analysis, showing that a 10 $\mu\text{g}/\text{m}^3$ increase in 60-month moving average of PM_{2.5} was associated with an elevated risk of COPD hospital visits of 1.11 [95% confidence interval (CI): 1.08, 1.14] (Table S7).

4. Discussion

In our retrospective cohort study using Korea health insurance data, long-term exposure to PM_{2.5} increased the risk of COPD development in the elderly population. A 10 $\mu\text{g}/\text{m}^3$ increase in 60-month moving average PM_{2.5} was associated with a 9% increase in COPD hospital visits. Stratification analysis by sex, age, and income groups; and diverse sensitivity analysis with different PM_{2.5} exposure levels, COPD definitions, and study period showed consistent results. The linear exposure–response relationship between PM_{2.5} and risk of COPD hospital visits was observed in concentration ranges over 30 $\mu\text{g}/\text{m}^3$.

One of the strengths of our study is the population based study sample. In contrast to previous cohort studies evaluating chronic exposure to air pollution and COPD mortality or COPD development using convenient samples (Andersen et al. 2011; Lepeule et al. 2012; Lipsett et al. 2011), we were able to perform an evaluation including almost all the elderly who have resided in the metropolitan cities in Korea. By using the diagnostic codes from the health insurance data, and focusing on the elderly residing in metropolitan city with high quality medical infrastructures, we were able to objectively define subjects with COPD. In addition, limited daily activities as well as commutabilities of the elderly add reliability to our PM_{2.5} exposure estimation, which were estimated based on the district level residential data.

Chronic exposure to ambient PM_{2.5} is linked to mortality due to ischemic heart disease, stroke, COPD, lung cancer, and acute respiratory infection (Cohen et al. 2017). However, although air pollution exposure may not lead to mortality, it may cause milder health complications in a large number of people (Samet and Krewski 2007). Therefore, studies focusing not only on mortality, but also on morbidity, are needed to quantify the accurate health burden attributable to ambient air pollution.

However, most of the previous ambient air pollution cohort studies dealing with COPD focused on mortality, showing mainly positive, but null associations were also observed in several studies. In an analysis of 7,805 subjects from the Harvard Six Cities study, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was found to be associated with an elevated risk of COPD mortality of 1.17 (95% CI: 0.85, 1.62) (Lepeule et al. 2012). Among 2.4 million persons from Canadian Census Health Environment Cohort, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with an elevated risk of COPD mortality of 1.24 (95% CI: 1.11, 1.39) (Pinault et al. 2017). In a follow-up of over 100,000 subjects from the California Teachers Study, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated with an elevated risk of non-malignant respiratory mortality of 1.21 (95% CI: 0.97, 1.52) (Lipsett et al. 2011). By following-up a population-wide sample of Oslo, Norway residents for 6 years, increased risk of COPD mortality was observed in subjects with the highest PM_{2.5} exposure (Næss et al. 2006).

In contrast, no association and inverse association, between PM_{2.5} exposure and COPD mortality were observed in several studies. In the Cancer Prevention II study, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} was associated

Table 1
Descriptive statistics of the study subjects in year 2008 (n = 687,940).

Variable	Total subject (n)	Average PM _{2.5} (2008–2010), Mean ± SE (µg/m ³)	Non-COPD cases, n (%)	Average PM _{2.5} (2008–2010), Mean ± SE (µg/m ³)	COPD cases, n (%)	Average PM _{2.5} (2008–2010), Mean ± SE (µg/m ³)
Total	687,940	31.2 ± 4.0	428,240	31.3 ± 4.0	259,700	31.0 ± 4.1
By sex						
Men	292,170	31.3 ± 4.0	176,929 (41.3)	31.4 ± 4.0	115,241 (44.4)	31.1 ± 4.1
Women	395,770	31.2 ± 4.0	251,311 (58.7)	31.2 ± 4.0	144,459 (55.6)	31.0 ± 4.1
By age group						
65–69	311,235	31.2 ± 4.0	185,001 (43.2)	31.4 ± 4.0	126,234 (48.6)	31.0 ± 4.2
70–74	197,218	31.2 ± 4.0	121,264 (28.3)	31.4 ± 4.0	75,954 (29.3)	31.0 ± 4.1
75–79	102,458	31.2 ± 4.0	66,183 (15.5)	31.3 ± 4.0	36,275 (14.0)	31.0 ± 4.1
80–84	50,125	31.1 ± 4.0	35,251 (8.2)	31.2 ± 4.0	14,874 (5.7)	31.1 ± 4.1
85–	26,904	31.3 ± 4.0	20,541 (4.8)	31.3 ± 4.0	6363 (2.5)	31.3 ± 4.0
By income group						
Q1 (lowest)	104,844	31.4 ± 4.1	64,726 (15.1)	31.6 ± 4.1	40,118 (15.5)	31.2 ± 4.2
Q2	92,622	31.1 ± 4.2	57,530 (13.4)	31.2 ± 4.1	35,092 (13.5)	30.8 ± 4.3
Q3	157,753	31.1 ± 4.1	97,472 (22.8)	31.2 ± 4.1	60,281 (23.2)	30.9 ± 4.2
Q4 (highest)	332,721	31.3 ± 3.9	208,512 (48.7)	31.3 ± 3.9	124,209 (47.8)	31.0 ± 4.0
By metropolitan city						
Seoul	306,295	34.2 ± 2.1	196,945 (46.0)	34.2 ± 2.1	109,350 (42.1)	34.3 ± 2.1
Busan	114,827	25.8 ± 1.9	65,047 (15.2)	25.8 ± 1.9	49,780 (19.2)	25.8 ± 1.9
Daegu	82,065	28.8 ± 1.3	51,199 (12.0)	28.9 ± 1.3	30,866 (11.9)	28.7 ± 1.3
Incheon	75,390	33.9 ± 3.7	47,319 (11.1)	33.7 ± 3.9	28,071 (10.8)	34.0 ± 3.5
Gwangju	41,379	28.0 ± 0.8	25,346 (6.0)	28.0 ± 0.8	16,033 (6.2)	28.0 ± 0.8
Daejeon	43,298	30.1 ± 0.2	28,321 (6.6)	30.1 ± 0.2	14,977 (5.8)	30.1 ± 0.2
Ulsan	24,686	26.4 ± 1.0	14,063 (3.3)	26.4 ± 1.0	10,623 (4.1)	26.4 ± 1.0
Contextual variables						
Proportion of high school diploma (%)	67.62 ± 4.97		67.63 ± 5.04		67.44 ± 4.84	
Proportion of current smokers (%)	24.7 ± 2.3		24.7 ± 2.3		24.8 ± 2.3	
Monthly average income (1,000KRW)	1,301 ± 83.0		1,303 ± 84.1		1,298 ± 81.0	
Standardized mortality rate per 100,000 persons	4584.7 ± 488.2		4577.0 ± 486.3		4597.4 ± 491.1	

with decreased risk of 0.84 (95% CI: 0.77, 0.93) for COPD and related deaths (Pope III et al. 2004). In a cohort study of 63,520 subjects in Japan, a 10 µg/m³ increase in PM_{2.5} was associated with decreased risk of 0.84 (95% CI: 0.77, 0.93) for COPD mortality, but the number of COPD deaths was very small (n = 64) (Katanoda et al. 2011). Null association in previous mortality studies may be partly due to under-diagnoses of COPD and different reporting patterns on the death certificates of each country (Schikowski et al. 2014). In particular, with negative association between chronic exposure to PM_{2.5} and COPD, but positive association with acute mortality outcomes such as pneumonia or influenza in Cancer Prevention II study; supports the hypothesis that COPD-related deaths may be coded as pneumonia or influenza deaths (instead of as COPD), which are common end-stage acute disease in COPD patients.

The studies evaluating the association between chronic exposure to air pollution and COPD hospital visits showed inconsistent results. In an analysis of 52,799 subjects from the Danish cohort, an interquartile

range increase in residential nitrogen dioxide and nitrogen oxides were associated with an elevated risk of COPD incidence of 1.08 (95% CI: 1.02, 1.14) and 1.05 (1.01, 1.10), respectively (Andersen et al. 2011). One cohort study of 812,063 patients from England found that an interquartile range increase in baseline PM_{2.5} showed a risk of 0.97 (95% CI: 0.71, 1.34) for the first general practitioner record of COPD, but an elevated risk of 1.31 (95% CI: 0.92, 1.86) for the first COPD admission (Atkinson et al. 2015). Among 467,994 subjects that resided in metropolitan Vancouver, Canada, an interquartile range increase in black carbon was associated with COPD hospitalization (RR: 1.06, 95% CI: 1.02, 1.10), but PM_{2.5} exposure showed null association (RR: 1.02, 95% CI: 0.98, 1.07) (Gan et al. 2013). In a Taiwanese cohort study with 91,709 subjects, a 5 µg/m³ increase in PM_{2.5} was associated with elevated risk of 1.08 (95% CI: 1.04, 1.11) for COPD development (Guo et al. 2018). Compared to the lower PM_{2.5} concentration observed in previous Western studies (mean PM_{2.5}: 4.1 to 12.9 µg/m³), the Taiwan cohort study involved relatively higher exposure level of PM_{2.5} (mean

Table 2
Average PM_{2.5} concentration (mean ± SE, µg/m³) by year and metropolitan city.

Year	Total	Seoul	Busan	Daegu	Incheon	Gwangju	Daejeon	Ulsan
2006	34.3 ± 9.9	38.1 ± 12.0	30.1 ± 7.5	30.9 ± 8.5	38.4 ± 10.2	33.6 ± 11.9	33.3 ± 12.8	27.9 ± 9.4
2007	33.9 ± 9.1	38.5 ± 10.2	29.3 ± 7.4	30.2 ± 8.8	37.6 ± 10.5	29.4 ± 10.4	33.9 ± 12.3	28.2 ± 8.9
2008	31.1 ± 6.5	34.8 ± 6.3	25.8 ± 6.0	31.9 ± 7.8	32.5 ± 7.5	29.6 ± 9.2	30.4 ± 9.1	28.3 ± 6.9
2009	30.5 ± 6.7	35.4 ± 7.5	25.6 ± 5.9	26.6 ± 6.1	33.2 ± 7.6	27.9 ± 7.9	29.7 ± 8.7	25.7 ± 6.1
2010	29.3 ± 7.7	32.7 ± 8.6	25.4 ± 6.0	28.5 ± 7.8	30.8 ± 9.0	25.9 ± 9.1	30.0 ± 10.2	25.6 ± 6.0
2011	28.3 ± 7.5	30.9 ± 8.9	25.7 ± 5.9	26.4 ± 6.4	29.8 ± 7.9	24.3 ± 7.5	29.8 ± 10.3	25.3 ± 6.6
2012	25.3 ± 5.7	27.1 ± 6.6	23.9 ± 4.4	23.8 ± 5.2	26.3 ± 6.7	21.6 ± 6.1	26.2 ± 8.5	24.2 ± 4.6
2013	28.5 ± 7.1	31.8 ± 7.9	24.4 ± 6.0	27.0 ± 8.0	27.2 ± 7.0	26.9 ± 10.3	31.9 ± 10.8	28.1 ± 6.6
2014	27.6 ± 8.0	32.2 ± 9.6	24.1 ± 7.3	25.0 ± 7.8	28.9 ± 7.4	19.8 ± 7.0	27.7 ± 11.3	25.1 ± 8.1
2015	25.3 ± 4.5	24.2 ± 4.8	25.9 ± 5.2	24.9 ± 5.2	27.6 ± 5.2	24.1 ± 4.2	27.3 ± 6.7	24.6 ± 5.3
2016	25.4 ± 4.5	26.1 ± 4.3	26.9 ± 5.8	23.9 ± 3.9	25.5 ± 4.4	22.6 ± 4.1	24.7 ± 6.4	23.3 ± 4.2
Total	29.0 ± 7.6	32.0 ± 9.1	26.1 ± 6.2	27.2 ± 7.3	30.7 ± 8.6	26.0 ± 8.8	29.5 ± 9.9	26.0 ± 6.7

Table 3

Hazard ratios (HR) for chronic obstructive pulmonary disease hospital visits for 10 $\mu\text{g}/\text{m}^3$ increases in $\text{PM}_{2.5}$ exposure.

	No.	Model 1 ^{a)}		Model 2 ^{b)}	
		HR	95% CI	HR	95% CI
60 month moving average exposure	259700/ 687940	1.10	1.08, 1.12	1.09	1.07, 1.11
48 month moving average exposure		1.10	1.08, 1.12	1.10	1.07, 1.12
Year 2008–2010 baseline exposure		1.08	1.06, 1.10	1.07	1.05, 1.10
Year 2008 baseline exposure		1.08	1.06, 1.10	1.07	1.04, 1.09

^{a)} Model 1: Stratified by age group and sex and adjusted for income group and metropolitan city

^{b)} Model 2: Stratified by age group and sex and adjusted for income group, metropolitan city, and district-level proportion of high school diploma (%), proportion of current smokers (%), monthly average income (1,000 KRW), and standardized mortality rate (per 100,000 person)

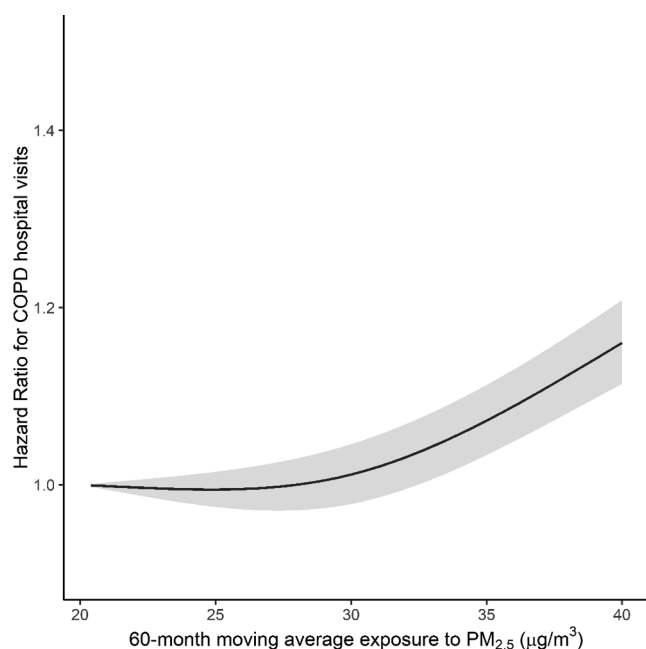


Fig. 2. Hazard ratio plot for chronic obstructive pulmonary disease hospital visits and 60-month moving average exposure to $\text{PM}_{2.5}$.

$\text{PM}_{2.5}$: 26.91 $\mu\text{g}/\text{m}^3$), similar to the $\text{PM}_{2.5}$ concentration observed in our study [mean $\text{PM}_{2.5}$ during the study period: 26.0 $\mu\text{g}/\text{m}^3$ (Gwangju and Ulsan, lowest) to 32.0 $\mu\text{g}/\text{m}^3$ (Seoul, highest)].

However, as highlighted in a previous review paper, the overall association between chronic exposure to air pollution and incidence of COPD is still inconclusive (Schikowski et al. 2014). It was pointed out in that previous paper that the use of hospital admission record may not be able to properly capture the real COPD incidence because hospital admission may incorporate acute exacerbation of previously diagnosed COPD cases. Because previous studies in Denmark, Canada, and England focused on hospital admission records only or partly, they were not free from COPD incidence case ascertainment issue. In addition, distinguishing the chronic from acute effects of air pollution on COPD development is challenging because short-term exposure to air pollution causes acute exacerbation of COPD, and short- and long-term exposure are highly correlated (Schikowski et al. 2014).

To partially address the COPD incidence case ascertainment issue, we did not separate the mode of visits, type of hospitals, and detailed medical service use in the analysis to specify the subjects with no prior

history of COPD hospital visits, and to capture all COPD-related hospital visits during the follow-up period. We also conducted sensitivity analysis by applying strict criteria (limiting the study subjects to persons with no prior COPD-related hospital visits for 6 years; using primary diagnostic codes to define COPD; defining the development of COPD as two or more hospital visits with COPD diagnosis) to define COPD development.

However, the ambiguous clinical course, with the slowly progressive nature of COPD, is challenging obstacles for the COPD case ascertainment. For example, some patients with COPD have no obvious clinical manifestations and can be diagnosed during a routine health examination. Because populations with high socioeconomic status are more likely to take health examinations, COPD patients can be more and quickly diagnosed in high-income populations. In our study, although the incidence rate of COPD hospital visits across income groups was similar (37 ~ 38%), we observed an increasing trend of HR with the increase of household income. This phenomenon may partially due to an early diagnosis and screening of COPD in high socioeconomic groups although p-value for interaction was not statistically significant.

Distinguishing the chronic from acute effects of air pollution is always a problem in air pollution studies and we may not be able to also rule out the possibility that both chronic and acute effects of air pollution on COPD hospital visits were incorporated in our study estimates. Additional studies using repeated spirometer measurements as well as hospital medical records with long duration of follow-up are needed.

The exposure–response curve between 60-month moving average $\text{PM}_{2.5}$ exposure and COPD hospital visits in our study is very similar to that of a previous Taiwanese study. In the previous study, increasing linear patterns of COPD incidence risks were observed at high $\text{PM}_{2.5}$ exposure ranges over 35 $\mu\text{g}/\text{m}^3$, although the risks were null between 20 and 35 $\mu\text{g}/\text{m}^3$ exposure range (Guo et al. 2018). Similar pattern was observed in our study showing increasing linear pattern at high exposure of over 30 $\mu\text{g}/\text{m}^3$, but no significant increase at $\text{PM}_{2.5}$ concentration exposure level between 20 and 30 $\mu\text{g}/\text{m}^3$ (Fig. 2). In contrast, $\text{PM}_{2.5}$ exposure and COPD mortality exposure–response curves in the Global Burden of Disease study and in a recent meta-analysis on air pollution cohort studies showed increasing linear patterns of COPD risk with increase in $\text{PM}_{2.5}$ concentration, for the entire $\text{PM}_{2.5}$ ranges (Burnett et al. 2018; Cohen et al. 2017). However, we were unable to determine the exposure–response curve in the lower ranges due to the high levels of $\text{PM}_{2.5}$ exposure in Korea.

Our study had several limitations. First, we were unable to adjust for personal level characteristics such as smoking, drinking, and exercise. Among diverse risk factors, smoking is the most important risk factor for COPD development. However, because our cohort was constructed based on health insurance claim data, we were unable to gather detailed personal level information. Although we used district level covariates to adjust for neighborhood and regional effects on subjects' health, further studies with better assessment of personal characteristics are needed to confirm our study findings. For instance, the proportion of current smokers in our study districts was around 25%, which makes it difficult to completely eliminate the effects of primary and second-hand smoking on COPD-related hospital visits without detailed personal level data. Therefore, additional stratification analyses and assessment of the exposure–response curves by baseline characteristics including smoking status are needed.

Secondly, we were unable to address previous hospital use data to evaluate other co-morbidities in our study subjects. Subjects with underlying chronic diseases may be more susceptible to long-term $\text{PM}_{2.5}$ exposure (Wang et al. 2017). However, we were unable to obtain access to data on other disease outcomes besides COPD in our analysis, due to NHIS data provision policy and the personal information protection act. In addition, although we evaluated data on all the elderly population aged over 65 years who resided in metropolitan cities in Korea, the elderly, residing in rural areas, were omitted in our study. Additional sensitivity analyses by excluding subjects with previous history of other

chronic diseases as well as studies in rural areas are required in the future. Thirdly, because we used modelled district-level ambient PM_{2.5} concentration as the exposure of interest, the effect of household PM_{2.5} concentration was ignored in our study. Because most of the study subjects were elderly people who may have longer indoor time activity patterns, our exposure levels may not properly capture the individual level exposure to PM_{2.5}. Future studies with household PM_{2.5} measurement are needed to estimate the association between personal level chronic exposure to PM_{2.5} and development of COPD. In addition, other air pollutants such as sulphur dioxide, black carbon, and nitric dioxide that have been shown to be associated with COPD hospital visits could not be evaluated in this study since the air pollution data was not available at district level resolution. Fourth, the diagnostic accuracy of COPD in health insurance data has not been evaluated. Although we used several definitions of COPD using diagnostic codes; and our study was conducted in metropolitan cities in Korea where medical quality has reached a certain level, such misclassification may have shifted our results toward the null.

By following 687,940 elderly subjects residing metropolitan cities in Korea for 6 years, we found that long-term PM_{2.5} exposure was associated with the development of COPD. A 10 µg/m³ increase in 60-month moving average PM_{2.5} was associated with 9% increase in COPD development. Additional studies using repeated spirometer measurements as well as hospital medical records are needed to confirm our study findings.

Funding

This research was supported by the National Strategic Project–Fine Particle of the National Research Foundation in Korea; funded by the Ministry of Science, Information, Communications, and Technology; the Ministry of Environment; and the Ministry of Health and Welfare (grant nos. 2017M3D8A1092008 and 2017M3D8A1092009), as well as the Center for Environmental Health through the Ministry of Environment.

CRediT authorship contribution statement

Changwoo Han: Conceptualization, Software, Formal analysis, Writing - original draft, Writing - review & editing. **Jongmin Oh:** Conceptualization, Data curation, Software. **Youn-Hee Lim:** Conceptualization, Methodology, Writing - review & editing. **Soontae Kim:** Resources. **Yun-Chul Hong:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study used the customized Health Insurance Data based on health insurance claims data in Korea. The aim and conclusion of this study are irrelevant to the National Health Insurance Service, Republic of Korea. The research number of this study is NHIS-2019-1-023.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105895>.

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